REMARKS

Claims 25 to 29 have been added and are supported by the application as filed, e.g., by claims 3, 4 and 18. Claim 24 has merely been rewritten as an independent claim. No new matter has been added. Claims 1-3, 5-16 and 18-29 will be pending upon entry of this amendment.

All the claims have been rejected under 35 U.S.C. § 103 as unpatentable in light of Hu et al. (1996) *Circulation Research* 78:492-498 (Hu) in view of Sitter et al. (1998) *J. Amer. Soc. Nephr.* 9:2005-2012 (Sitter). The rejection is respectfully traversed.

The pending claims are directed to a method of treating permeability failure in a subject. As recited in claim 1, the method includes introducing into the subject a peritoneal dialysis fluid which includes a specific inhibitor of PKC. Dependent claims limit the specific inhibitor of PKC to a specific inhibitor of certain PKC isozymes, e.g., PKCβ or β1. The Examiner alleges that,

> Although Sitter et al. do not teach of other inhibitors of PKC it would have been obvious to one having ordinary skill in the art to substitute one PKC inhibitor for another since Sitter et al. are directed to the synthesis of prostaglandin E2. The skilled artisan would have been motivated to substitute on (*sic*) PKC inhibitor, such as Ro 31-8220, for another PKC inhibitor, namely bisindolylmaleimide, because Hu et al. teach that bisindolylmaleimide is a highly selective PKC inhibitor.

Applicants disagree. The Examiner has not made a *prima facie* case because to establish *prima facie* obviousness of a claimed invention, "the prior art reference (or references when combined) must teach or suggest all the claim limitations." (See MPEP § 706.02(j), emphasis added). As discussed below, neither Sitter nor Hu, alone or in combination, teach or suggest adding to dialysis fluid a specific PKC inhibitors as recited in the claims. Moreover, neither Sitter nor Hu even mention the specific isoforms of PKC as recited in the claims or suggest a role for these particular isoforms in permeability failure. Thus, not only is the combination of Sitter and Hu improper because there is no suggestion or motivation in the art to combine the references as the Examiner has done, but even if combined, the references do not provide the suggestion or motivation to make a dialysis fluid that includes the specific PKC inhibitors recited in the claims.

Sitter

Sitter merely discloses exposing cultured cells to Ro 31-8220. Ro 31-8220 is not a specific inhibitor of PKC. In fact, Ro 31-8220 inhibits several protein kinases other than PKC. Namely, Ro 31-8220 inhibits MAPKAP kinase-1β (also known as Rsk-2) more potently than it inhibits mixed PKC isoforms, and it also inhibits p70 S6 kinase (see Alessi (1997) *FEBS Lett.* 402:121-123, abstract, submitted as Appendix A with the last reponse). The fact that Ro 31-8220 is not a specific PKC inhibitor has been confirmed in other studies (see, e.g., Guo et al. (1999) *Am. J. Physiol.* 276:C435-41, abstract (Appendix B submitted with last response). Further, as the Examiner acknowledges, "Sitter et al. are silent to other inhibitors of PKC" (Office Action, page 2, paragraph 6). Therefore, Sitter does not provide a teaching or motivation to use any other inhibitors of PKC, much less a specific inhibitor of PKCβ, β1 or LY333531. The Examiner is left only with Hu to provide the missing teaching or suggestion.

Hu

Hu discloses the use of bisindolylmaleimide as an *in vitro* reagent to show that PKC activates ATP-sensitive K+ current in ventricular myocytes. Hu does not use bisindolylmaleimide in a method of treating anything, much less treating permeability failure. In fact, Hu et al. has nothing whatsoever to do with dialysis fluid. Moreover, Hu does not even mention specific isoforms of PKC involved in activating ATP-sensitive K^+ current, much less specific isoforms involved in permeability failure. Therefore, Hu cannot provide the teaching or suggestion missing from Sitter.

Hu and Sitter combined

The MPEP plainly states that "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP § 2143.01. It is insufficient that one reference theoretically can be combined with another. As discussed above, there is no suggestion in either Sitter or Hu that it would be desirable to substitute the PKC inhibitor disclosed in Hu in the method of Sitter. A suggestion or motivation is simply not present. Instead, Sitter et al. disclose an inhibitor of many different protein kinases and provide no suggestion or motivation to focus on a particular protein kinase or specific isoforms of that kinase to treat permeability failure. Hu et al. add nothing to remedy this deficiency.

Neither does the general knowledge in the art provide the necessary motivation or suggestion. Contrary to the Examiner's contention, a skilled artisan would surely not be motivated to arbitrarily substitute one PKC inhibitor for another. Some specific PKC inhibitors are further specific to a single PKC isozyme and PKC isozymes are known to play distinct, and in some cases, opposing roles in the transduction of intracellular signals. PKC inhibitors are clearly not arbitrarily interchangeable. In this instance, the Examiner has randomly chosen a reference that discloses a specific PKC inhibitor and combined it with Sitter. This is impermissible hindsight. Without a suggestion or motivation in the art to combine the references cited, the references may not be combined to support a finding of obviousness.

In as much as there is no suggestion or teaching for combining the references proposed by the Examiner, and that such a combination even if properly made would not result in the invention as claimed, Applicant respectfully submits that the references do not support a *prima facie* case of obviousness under the provisions of 35 USC §103. Therefore, Applicant respectfully contends that all the pending claims are patentably distinguishable over the prior art of record. The application is considered to be in condition for allowance and an early indication of same as earnestly solicited.

Attached is a marked-up version of changes made. Enclosed is a check for the amount of $27 for excess claims fees. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing the attorney docket number indicated above.

Respectfully submitted,

Date: 10/23/01

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Version with markings to show changes made

In the claims:

Claim 24 has been amended as follows:

24. (Amended) A method of making an improved peritoneal dialysis fluid, comprising: providing a peritoneal dialysis fluid and adding [The method of claim 23, wherein said inhibitor is] LY333531 to the dialysis fluid.

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1: FEBS Lett 1997 Feb 3;402(2-3):121-3 Related Articles, Books

The protein kinase C inhibitors Ro 318220 and GF 109203X are equally potent inhibitors of MAPKAP kinase-1beta (Rsk-2) and p70 S6 kinase.

Alessi DR.

Department of Biochemistry, University of Dundee, UK.

The protein kinase C (PKC) inhibitors Ro 318220 and GF 109203X have been used in over 350 published studies to investigate the physiological roles of PKC. Here we demonstrate that these inhibitors are not selective for PKC isoforms as was previously assumed. Ro 318220 inhibited MAPKAP kinase-1beta (also known as Rsk-2) in vitro (IC50 3nM) more potently than it inhibited mixed PKC isoforms (IC50 5 nM), and it also inhibited p70 S6 kinase (IC50 15 nM). GF 109203X also potently inhibited MAPKAP kinase-1beta (IC50 50 nM) and p70 S6 kinase (IC50 100 nM) with similar potency to PKC isoforms (IC50 30 nM). The inhibition of MAPKAP kinase-1beta, p70 S6 kinase, and probably other protein kinases, may explain many of the effects previously attributed to PKC.

PMID: 9037179 [PubMed - indexed for MEDLINE]

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1: Am J Physiol 1999 Feb;276(2 Pt 1):C435-41 Related Articles, Books, LinkOut

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Resistance to TNF-alpha cytotoxicity can be achieved through different signaling pathways in rat mesangial cells.

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We reported previously that Ro-318220 blocked expression of mitogen-activated protein kinase phosphatase-1 (MKP-1) induced by tumor necrosis factor-alpha (TNF-alpha) and subsequently caused apopotosis in mesangial cells (Y.-L. Guo, B. Kang, and J. R. Williamson. J. Biol. Chem. 273: 10362-10366, 1998). These data support our hypothesis that a TNF-alpha-inducible phosphatase may be responsible for preventing sustained activation of c-Jun NH2-terminal protein kinase (JNK) and consequent cell death in these cells (Y.-L. Guo, K. Baysal, B. Kang, L.-J. Yang, and J. R. Williamson. J. Biol. Chem. 273: 4027-4034, 1998). In this study, we investigated the involvement of protein kinase C (PKC) in regulation of MKP-1 expression in mesangial cells together with effects on viability. Although originally characterized as a PKC inhibitor, Ro-318220 inhibited TNF-alpha-induced MKP-1 expression through a mechanism other than blocking the PKC pathway. Furthermore, inhibition of the PKC pathway neither significantly affected TNF-alpha-induced MKP-1 expression nor made cells susceptible to toxic effect of TNF-alpha. Thus PKC activation is not essential for cells to achieve the resistance to TNF-alpha cytotoxicity displayed by normal mesangial cells. However, activation of PKC by phorbol 12-myristate 13-acetate (PMA) dramatically increased cellular resistance to the apoptotic effect of TNF-alpha. Coincidentally, PMA stimulated MKP-1 expression and suppressed JNK activation. Therefore, PMA-induced MKP-1 expression may contribute to the protective effect of PMA. These results provide a mechanistic explanation for previous documentation that PKC activation can rescue some cells from apopotosis.

PMID: 9950771 [PubMed - indexed for MEDLINE]